

## Innate Immune Regulation of Lung Alveolar Stem Cell Renewal in Mouse and Man

### Grant Award Details

Innate Immune Regulation of Lung Alveolar Stem Cell Renewal in Mouse and Man

**Grant Type:** Basic Biology V

**Grant Number:** RB5-07302

**Project Objective:** The mechanisms that regulate mature alveolar epithelial stem cell renewal are unknown. The Noble lab has developed state-of-the-art tools to target both mature alveolar type 2 (AEC2) and mesenchymal cell populations and map the fate of these populations in the context of noninfectious lung injury. Mice deficient in either TLR4 or with a targeted deletion of hyaluronan synthase 2 (HAS2) in AEC2 cells are enormously sensitive to non-infectious lung injury and develop fulminant interstitial fibrosis. AEC2 cells isolated from the mice deficient in either TLR4 or with a targeted deletion of HAS2 show a reduced self-renewal capacity. Preliminary studies have led to the hypothesis that interactions between components of the innate immune system expressed by AEC2 and the cell surface glycosaminoglycan hyaluronan are essential for stem cell renewal and lung repair after injury, and loss of this interaction results in severe lung fibrosis. The lab intends to define the mechanisms by which innate immune components TLR4, MyD88 and NF- $\kappa$ B expression, as well as HAS2 in AEC2 cells promote progenitor cell renewal and lung repair in vivo and in vitro. The operating hypothesis is that AEC2 cells from IPF patients have impaired stem cell renewal capacity. The role of the TLR4-HAS2 axis in AEC2 progenitor cell renewal in cells isolated from patients with IPF compared with normal lung will be determined.

**Investigator:**

<b>Name:</b>	Paul Noble
<b>Institution:</b>	Cedars-Sinai Medical Center
<b>Type:</b>	PI

**Award Value:** \$617,662

**Status:** Closed

### Progress Reports

**Reporting Period:** Year 1

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**Reporting Period:** Year 2

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## Grant Application Details

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**Application Title:** Innate Immune Regulation of Lung Alveolar Stem Cell Renewal in Mouse and Man

**Public Abstract:** The lung, along with the skin and gut are the three organs in perpetual contact with our environment. The lung has evolved mechanisms for repairing injury due to exogenous noxious agents. The timely repair of lung injury is essential and determines the outcome of life or death. The mechanisms that regulate mature alveolar epithelial stem cell renewal are unknown. Our preliminary studies have led to the hypothesis that interactions between components of the innate immune system expressed by lung alveolar epithelial cells and the cell surface glycosaminoglycan hyaluronan are essential for stem cell renewal and lung repair after injury, and loss of this interaction results in severe lung fibrosis. In this proposal, we will define the mechanisms by which innate immune components, as well as endogenous matrix in lung alveolar epithelial cells promote progenitor cell renewal and lung repair. This is the first link between innate immunity and lung stem cell renewal. Elucidating the mechanisms by which endogenous matrix and innate immune components interact to promote stem cell renewal could lead to novel therapeutic approaches to lung diseases.

**Statement of Benefit to California:** Our proposed study is to elucidate the mechanisms by which endogenous matrix and innate immune components interact to promote stem cell renewal which is critical for repair of injured lung. Achievement of the goals of this application will result in a completely novel approach to the treatment of lung diseases. Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease for which no effective medical therapies exist. Thousands of Californians suffer from pulmonary fibrosis. Lung transplant is the only therapy to prolong life. If the aims of this proposal are achieved, the concepts that drive this field will be changed by demonstrating that fibrotic lung disease can be treated by restoring essential signals necessary for lung stem cell renewal.

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